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Retraction

Patricia Vuijk 1, Pol A.C. van Lier 1,2, Anja C. Huizink 1, Frank C. Verhulst 1, Alfons A.M. Crijnen (2006). Prenatal smoking predicts non-responsiveness to an intervention targeting attention-deficit/hyperactivity symptoms in elementary schoolchildren. *The Journal of Child Psychology and Psychiatry* 47(9), 891–901.

The above article, published online on 22 August 2006, has been retracted by agreement between the Journal Editor-in-Chief, Tony Charman, ACAMH and Blackwell Publishing Ltd. After notifying the authors, the retraction has been agreed due to a concern surrounding the accuracy of some of the data that was not possible to resolve between the authors.

Tony Charman
Editor-in-Chief

The Journal of Child Psychology and Psychiatry

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RETRACTED

Prenatal smoking predicts non-responsiveness to an intervention targeting attention-deficit/hyperactivity symptoms in elementary schoolchildren

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Background: Some evidence suggests that prenatal exposure to maternal smoking contributes to the etiology of Attention-Deficit/Hyperactivity Disorder (ADHD). The present study tested an intervention targeting disruptive behavior to establish whether exposure to maternal smoking during pregnancy predicts intervention failure in elementary schoolchildren. **Methods:** Five hundred and eight elementary schoolchildren were followed from ages 7 to 11. At ages 8 and 9, they were randomly assigned to a control condition, or to a two-year universal classroom-based intervention targeting disruptive behavior. Measures included maternal reports of smoking during pregnancy, teacher-rated symptoms of ADHD from ages 7 to 9 years, and children's self-report of experimentation with smoking at ages 10 and 11 years. **Results:** At age 7, prenatally exposed children had higher ADHD symptom scores. The intervention did not affect the course of their ADHD symptoms and the probability of early-onset experimentation with smoking. Among non-exposed children, the intervention positively affected the course of ADHD symptoms, and reduced the probability of early-onset experimentation with smoking. **Conclusions:** Prenatally exposed children are most prone to follow a path of high levels of ADHD symptoms and associated elevated risk for early-onset experimentation with smoking, which is unreceptive to a universal preventive intervention. In these children, the developmental course of ADHD symptoms seems to have been influenced by their prenatal exposure to maternal smoking. Future research should further explore whether prenatal smoking is a proxy measure that indexes another risk factor, or a causal factor for adverse developmental outcomes. **Keywords:** Prenatal smoking, fetal programming, preventive interventions, ADHD symptoms, early-onset experimentation with smoking.

According to the concept of developmental programming, 1) particular experiences have a lasting influence on the structural and functional development of the organism, an influence that 2) will persist despite any beneficial changes that occur in the environment during a later developmental phase (Rutter, 2002). Similarly, stimuli or insults during fetal life that have lasting or lifelong effects can be regarded as fetal programming (Barker, 1998). Prenatal exposure to maternal smoking, which is thought to affect the development of children, has thus been a focus of recent studies.

Several studies that accord with the fetal programming hypothesis have found associations between prenatal exposure to maternal smoking and various problems in offspring: attention-deficit/hyperactivity problems (Button, Thapar, & McGuffin, 2005; Rodriguez & Bohlin, 2005; Thapar et al., 2003; for a review, see Linnet et al., 2003), conduct disorder (for a review, see Wakschlag, Pickett, Cook, Benowitz, & Leventhal, 2002), delinquency (Brennan, Grekin, Mortensen, & Mednick, 2002), and early-onset experimentation with smoking (Cornel-

ius, Leech, Goldschmidt, & Day, 2000; Milberger, Biederman, Faraone, Chen, & Jones, 1997). To date, however, no study has tested whether the reported association between smoking during pregnancy and behavioral problems in offspring persists despite beneficial changes in the environment. The present study therefore aimed to test whether the hypothesized developmental chain of prenatal exposure to maternal smoking, which results in the development of childhood symptoms of attention-deficit/hyperactivity disorder (ADHD) and associated elevated risk for early-onset experimentation with smoking, would persist after systematically changing the child's environment by a universal, classroom-based preventive intervention.

Fetal exposure to maternal smoking is thought to be linked to childhood behavioral problems through influences on early brain development (Ernst, Moolchan, & Robinson, 2001). Support for a causative link between prenatal exposure to maternal smoking and a deleterious effect on brain development is shown in animal models where nicotine, one of the many compounds of cigarettes, has been found to be a 'neuroteratogen' (Slotkin et al., 2005). These animal studies also demonstrated that prenatal nicotine

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exposure causes long-lasting ADHD-like symptoms in offspring (Pauly, Sparks, Hauser, & Pauly, 2004).

Several studies have sought to test the plausibility of this hypothesized pathway in humans by testing whether this association was confounded by environmental and heritable risks. Using genetically informative samples, two recent studies examined whether prenatal exposure to smoking, in addition to genetic liability to problem behavior and correlated environmental risk factors (low birth weight, low socio-economic status, antisocial traits and psychopathology in parents, harsh parenting practices, and women's use of alcohol and drugs during pregnancy), predicted offspring problem behavior. Both studies found that, although genetic liability and the correlated environmental risk accounted for much of the association, prenatal smoking still uniquely predicted offspring ADHD symptoms (Thapar, Holmes, Poulton, & Harrington, 1999), as well as conduct problems (Maughan, Taylor, Caspi, & Moffitt, 2004). These results support the first part of the fetal programming hypothesis that prenatal smoking has a lasting influence on a child's structural and functional development.

The aim of the present study was to test the second part of the fetal programming hypothesis by examining whether the effect of prenatal exposure to maternal smoking persisted despite the beneficial changes intervention brings to a child's environment. To test the association between prenatal exposure to maternal smoking, the development of childhood ADHD symptoms (from age 7 to age 9), and the associated risk for early-onset experimentation with smoking (at age 10 and 11), we used an ongoing preventive intervention trial. Specifically, in a population-based sample of 508 Dutch elementary schoolchildren, we tested whether prenatal exposure to maternal smoking moderated the effectiveness of the Good Behavior Game (GBG; Dolan, Jaylan, Werthamer, & Kellam, 1989), a classroom-based, preventive intervention targeting disruptive behavior, which has been adapted for use in the Netherlands by the educational services (van der Sar & Goudswaard, 2001).

The GBG has already been shown to be effective in reducing attention-deficit/hyperactivity problems (van Lier, Muthén, van der Sar, & Crijnen, 2004), aggressive behavior (i.e., Ialongo, Poduska, Werthamer, & Kellam, 2001), antisocial behavior (van Lier, Vuijk, & Crijnen, 2005), and early-onset smoking (Storr, Ialongo, Kellam, & Anthony, 2002). Given the hypothesized influence of maternal smoking on early brain development, and associated elevated risks for ADHD symptoms and early-onset smoking, we reasoned that prenatally exposed children 1) would show higher levels of ADHD symptoms after controlling for environmental confounders, 2) would be unreceptive to a positive impact of the GBG on the development of ADHD symptoms, 3) would subsequently have a higher risk for early-onset

experimentation with smoking, and 4) would be unreceptive to the – indirect – impact of the GBG on early-onset experimentation with smoking.

Methods

Participants

Participants were part of a longitudinal intervention study targeting disruptive behavior. Mainstream elementary schools in the metropolitan area of Rotterdam and Amsterdam were eligible for inclusion. The first 13 schools that responded positively to the invitation to participate were included. In these schools, 794 children attending first grade (age 6) were assessed in the spring of 1999. Of those who moved on to second grade (age 7), 722 were eligible for inclusion. Twenty-two children who repeated second grade in 1999 and moved into the study cohort were included in the sample for intervention purposes, making a total sample of 744 children. Of these children, 666 parents or parent substitutes (89.5%) signed written informed consent granting the child permission to participate in the study. Thirty-one percent of the sample was of low socio-economic status, which was consistent with the Dutch population (Statistics Netherlands, 1999).

Figure 1 shows a flowchart in which the dropouts are presented for each step. During the 2-year intervention period in grades 2 and 3 (age 7 and 8), 92 children were lost to follow-up because they moved away from a study school before participating in the follow-up measures. During the follow-up measures in grades 4 and 5 (age 9 and 10), one school ($n = 55$) dropped out of the study. In the case of eleven more children, language problems of the mother meant that data about mother's smoking during pregnancy and current parental smoking was unavailable. Dropout in these 66 children was not significantly related to the child's gender ($\chi^2(1, N = 574) = .51, p > .05$), teacher ratings of ADHD symptoms at age 7 ($F(1, 540) = .72, p > .05$), and maternal psychopathology ($F(1, 532) = .24, p > .05$). However, children who dropped out of the study cohort were predominantly of non-Caucasian ethnicity ($\chi^2(1, N = 574) = 40.40, p < .01$), and of low socio-economic status ($\chi^2(1, N = 533) = 33.48, p < .01$). Characteristics of the sample included in this study are presented in Table 1.

Intervention

The GBG is a classroom-based behavior management strategy that promotes prosocial behavior and reduces disruptive behavior. Teachers and students choose positively formulated class rules, which are accompanied by pictograms. At the beginning of the GBG cycle, teachers assign children to one of three or four teams, each containing equal numbers of disruptive and non-disruptive children. Children are encouraged to manage their own and their team-mates' behavior. Each team receives a number of cards, one of which will be taken by the teacher when a team-member violates a rule. Teams are rewarded when, at the end of the game, at least one card remains, while all students are always rewarded with compliments throughout the game.

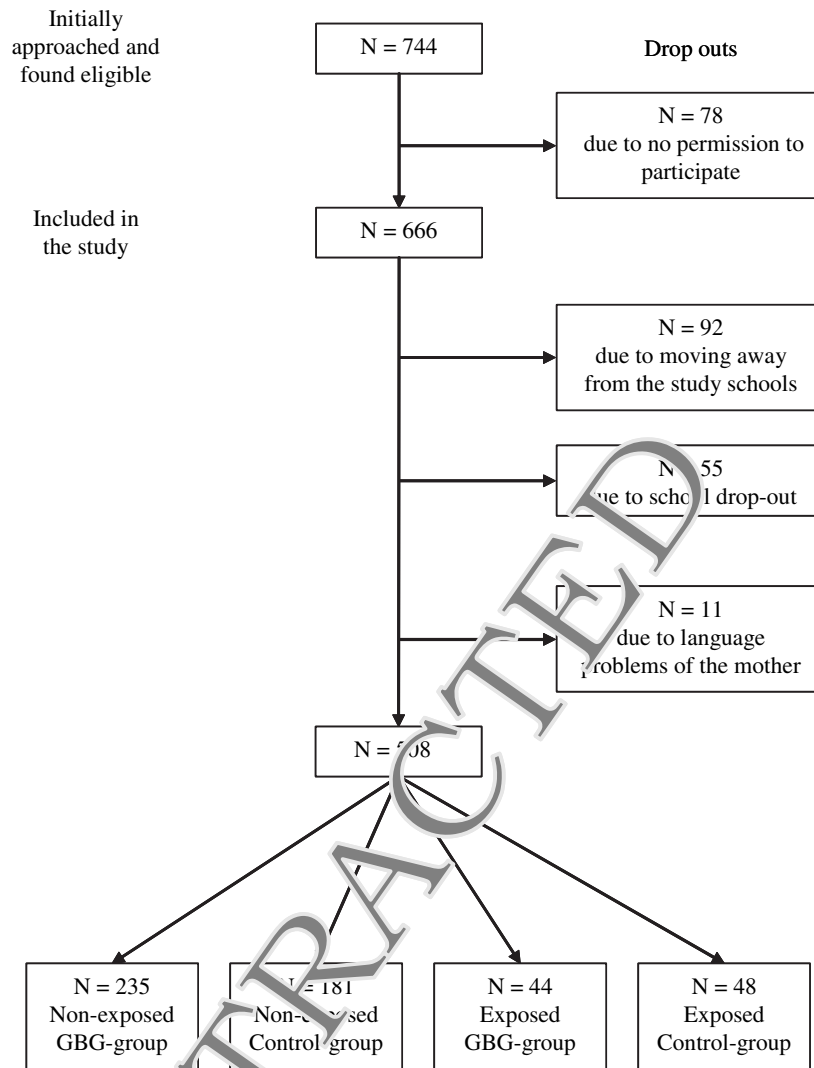


Figure 1 Number of included participants

Table 1 Characteristics of non-exposed and exposed GBG and control group children

	Non-exposed (n = 416)		Exposed (n = 92)	
	Control	GBG	Control	GBG
Male gender (%)	51	55	60	50
Caucasian (%)	81	80	82	91
Low SES (%)	34	28	46	30

Note: No differences between exposed and non-exposed or GBG and Controls were found. SES = socio-economic status.

Initially, winning teams also receive tangible rewards directly after each game. Later on, winning teams receive delayed rewards.

The GBG was implemented in three different stages. In the *introduction* stage, which started in the second grade in fall, it was played three times a week for 10 minutes. In the *expansion* stage, it was extended with regard to time and settings, and also to the behaviors targeted. Rewards were delayed until the end of the week and month. This phase lasted until the early spring of the school year. In the third stage – the

generalization stage – the emphasis lay on explaining to children that the GBG rules also apply in various other settings.

The GBG was implemented in second and third grade. Both years, teachers received eight hours of training on its implementation. In class, they were also coached by the school advisory services in ten 60-minute classroom observations. External school advisors assessed the fidelity of implementation; per class, this was based on the frequency with which the GBG was performed, as well as the total number of hours it was performed. This led to an implementation fidelity score at three levels: 'good', 'average', or 'bad'. Differences in implementation fidelity were not related to the mother's smoking status during pregnancy (χ^2 (2, $N = 276$) = 3.71, $p > .05$).

Design

In 1999, each of the schools had at least two first grade classes, which is where the baseline assessments were completed. During the summer break, when second grade class compositions were known, classes within one school were randomly assigned to either the inter-

vention or control condition. The GBG intervention started in fall in the second grade. Over the two-year intervention period, the composition of the class remained the same for 90.4% of the children.

Measures

Women's use of cigarettes during pregnancy was assessed by means of a standard interview, the Substance Use during Pregnancy Interview (SUPI; Erasmus MC, 2002). When the children were 10 years old, trained interviewers contacted the mothers by telephone for information on the number and frequency of cigarettes they had smoked during pregnancy.

Teacher-reported child behavior problems over the last two months were assessed using the Teacher's Report Form/6-18 (TRF/6-18; Achenbach, 1991), which has been translated and validated for use in the Netherlands (Verhulst, van der Ende, & Koot, 1997), and which contains a list of 120 items whereby a child's behavior is rated on a three-point scale. The TRF/6-18 was completed at baseline, and at 12-month and 24-month assessments. Items from the Attention Problem scale were used. Items included 'This child can't sit still, is restless, or hyperactive' and 'This child has difficulty following directions'. Cronbach's α ranged from .90 to .91 over the assessments. Teachers received a gift certificate for their participation.

Teacher-reported problem behavior at school was assessed using the Problem Behavior at School Interview (PBSI; Erasmus MC, 2000a), a 32-item interview assessing disruptive behavior and shy/withdrawn behavior in children. Teachers rated each child's behavior on a 5-point Likert scale. Research assistants interviewed the teachers at the 18-month and 24-month assessment. In this study, only the ADHD symptoms scale was used, which consists of eight items, including 'this child has difficulty with concentration' and 'this child is impulsive'. Cronbach's α were .93 and .94.

Information on *children's early-onset experimentation with smoking* was obtained using the Substance Use Questionnaire (SUQ; Erasmus MC, 2000b), which contains self-report items regarding children's experimentation with smoking at ages 10 and 11. The Substance Use Questionnaire was filled out in the classroom. The children were told that their answers would be confidential and that they did not have to answer any of the questions if they did not want to.

Confounding variables

Variables were assessed through a parent interview that was conducted before the start of the intervention (at age 7).

Low socio-economic status (SES) was based on the highest parental occupation and highest level of education completed within a family. Low SES was defined as unemployment, the performance of work requiring minimal education and/or having completed only elementary school or less (Statistics Netherlands, 1999).

Maternal psychopathology was assessed using the Dutch translation of the General Health Questionnaire – 28 item version (GHQ-28; Goldberg, 1972; Koeter & Ormel, 1991), which has demonstrated adequate

psychometric properties for use in the Netherlands (Koeter & Ormel, 1991), and which consists of four 7-item scales measuring Somatic Symptoms, Anxiety/Insomnia, Social Dysfunction, and Severe Depression. Mothers rate their mental health over the last two weeks on a 4-point Likert scale. Following the procedure of Goldberg and Williams (Goldberg & Williams, 1988), the scoring was transformed into a yes/no format by recoding the original codes. Thus 0 ('better than usual') and 1 ('same as usual') became 0 ('no'); and 2 ('worse than usual') or 3 ('much worse than usual') became 1 ('yes'). All items were then summed to a total score. High maternal psychopathology was defined as having a total score of 5 or higher. According to this definition, 21% of the sample had a high score for maternal psychopathology.

Harsh parenting practices were assessed using the Alabama Parenting Questionnaire (APQ; Shelton, Frick, & Wootton, 1996), a 42-item questionnaire in which parents use a 5-point Likert scale to rate how often they display the described parenting behavior. In our analyses, only the Corporal Punishment (Cronbach's $\alpha = .54$) and Inconsistent Discipline (Cronbach's $\alpha = .53$) scales were used.

Women's use of alcohol during pregnancy was assessed through the Substance Use during Pregnancy Interview (SUPI; Erasmus MC, 2002). Mothers were asked whether they had used alcohol during the pregnancy. Only 4.2% of the mothers indicated that they had done so.

Current parental smoking and birth weight were assessed during the telephone interview when children were 10 years old. At the time of the assessment, parents were asked if they still currently smoked, current smoking being defined as a dichotomized variable: 0 ('no') if they did not currently smoke and 1 ('yes') if they did. Low birth weight was defined as a birth weight of 2500 grams or less.

Statistical approach

The model used to analyze ADHD symptoms is shown in Figure 2. Items from the TRF/6-18 and PBSI reflecting similar content were selected, resulting in the selection of eight ADHD symptoms from both the TRF and PBSI. These items were summed to a total ADHD symptoms score (TRF at baseline, 12 and 24 months; PBSI at 18 and 24 months).

To account for the missing-by-design data, the following procedure was used. First, a latent variable was considered for each of the four time-points (baseline, 12-, 18-, and 24-month follow-up), which served as the indicators for the growth factors (intercept and slope). Indicators for these latent variables were the total ADHD symptom scores derived from the TRF and PBSI at the given time-points. Second, measurement invariance of ADHD symptoms across the four time-points was approached as follows: a) To put the four latent ADHD problem variables in the same metric at each of the four time-points, the factor loading of the TRF on the latent variables at each time-point was set by default at 1; the factor loading for PBSI was held equal across time. b) The measurement intercepts were held to be equal across time for both the TRF and PBSI scores.

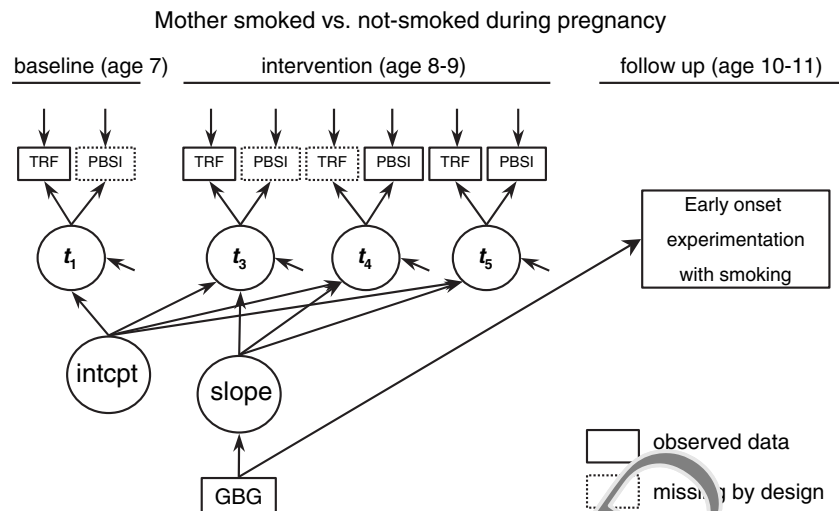


Figure 2 Observed and latent variables to analyze the impact of the GBG intervention on the development of ADHD symptoms and early-onset experimentation with smoking

To test the hypothesis that levels of ADHD symptoms at elementary school entry were higher for prenatally exposed children, we first estimated the direct effect of smoking during pregnancy on the intercept of ADHD symptoms, also controlling for the hypothesized confounding factors (current parental smoking, low socioeconomic status, maternal psychopathology, harsh parenting practices, women's use of alcohol during pregnancy, and low birth weight).

Then, to explore whether the developmental course of exposed and non-exposed children was receptive to change, we used Growth Mixture Modeling (GMM; Muthén, 2001) to study the impact of the GBG on the development of ADHD symptoms and on the probability of early-onset experimentation with smoking. Two classes were defined, one for prenatally exposed children, and one for non-exposed children. For each class of children, GMM estimates mean growth curves, i.e., initial status (intercept) and change (slope), and captures individual variation around these growth curves by estimating factor variances for each class. The slopes of the developmental trajectories of the two classes were regressed on intervention status (Muthén, 2002). Probability of smoking at age 10 and 11 years was included as a distal outcome in the model, and regressed on intervention status. Male gender and current parental smoking were included in the model to control for possible gender influences on the growth parameters and impact of the GBG intervention. All analyses were performed with Mplus 3.0 (Muthén & Muthén, 1998–2004).

Results

Descriptive statistics

During their pregnancy with the target children, 18% of the mothers had smoked ($n = 92$), a figure approximately similar to that of the general Dutch population (Crone, Hirasing, & Burgmeijer, 2000). Of these mothers, 62% had smoked 1 to 9 cigarettes per day, 25% had smoked 10 to 19 cigarettes per

day, and 13% had smoked over 20 cigarettes per day. The percentage of children exposed was similar between GBG and control-group children ($\chi^2(1, N = 508) = .15, p > .05$). Thirteen percent of the children reported early-onset experimentation with smoking at ages 10 and 11 ($n = 67$), which is about the same as in the general Dutch population (Monshouwer, van Dorsselaer, Gorter, Verdurmen, & Vollebergh, 2004). The percentage of early-onset smokers was similar among prenatally exposed and non-exposed children ($\chi^2(1, N = 502) = .16, p > .05$).

Smoking during pregnancy and ADHD symptoms at age 7

Smoking during pregnancy had a significant impact on the intercept of the development of ADHD (see Table 2), indicating a higher level of ADHD symp-

Table 2 Parameter estimates of simple and multiple regression coefficients of risk variables on the level of ADHD symptoms at age seven

Risk variables	Parameter estimates			
	Simple		Multiple	
	Est.	SE	Est.	SE
Pregnancy				
Low birth weight	-1.0	.7	–	–
Smoking	1.1	.4*	.9	.4*
Alcohol use	-1.2	.8	–	–
Male gender	1.5	.3**	1.5	.3**
Family/parenting				
Maternal psychopathology	.2	.4	–	–
Inconsistent Discipline	1.0	.4*		
Harsh parenting	1.3	.4**	.8	.4*
Contextual				
Low SES	1.3	.3**	1.2	.3**

Note: Est = Estimate. SE = Standard Error. SES = socio-economic status. * $p < .05$. ** $p < .01$.

toms in prenatally exposed children. To account for possible confounding factors, we included male gender, alcohol use during pregnancy, maternal psychopathology, low birth weight, harsh parenting practices, and low SES in the model. The potential confounding factors were first tested individually. Parameter estimates are presented in Table 2. Only male gender, harsh parenting, inconsistent discipline, and low socio-economic status were significantly associated with the intercept of ADHD symptoms. These risk factors, including smoking during pregnancy, were then submitted to a multiple regression model, in which all the significant predictors from the simple regression models remained significant (see Table 2).

ADHD symptoms development, early-onset experimentation with smoking, and GBG impact

We then tested whether the course and malleability of ADHD symptoms and the probability of early-onset experimentation with smoking were different for exposed and non-exposed children. The developmental courses of exposed and non-exposed children were analyzed simultaneously. The slope of ADHD symptoms and early-onset experimentation with smoking at ages 10 and 11 were regressed on intervention status for both exposed and non-exposed children. To control for possible confounding of male gender and current parental smoking, both the main effects and the interaction with GBG impact were included in the model. Neither of the two interaction terms, nor the main effect of current parental smoking was significant. They were thus excluded from the model. The course of ADHD symptoms for both groups of children is displayed in Figure 1. The impact of the GBG intervention on the parameter estimates and the effect of male gender on the parameter estimates are presented in Table 3.

From ages 7 to age 9, exposed children had stable high levels of ADHD symptoms (slope estimate: $b = .081$, $\beta = .99$, $SE = .76$, $p > .05$), levels of ADHD symptoms being higher in boys than in girls (see Table 3). The estimate of intervention status on the

slope of ADHD symptoms was not significant, indicating no impact of the GBG on the development of ADHD symptoms in these exposed children. By ages 10 and 11, 15% of the exposed control-group children and 19% of the exposed GBG children had experimented with smoking. The difference in this percentage was not statistically significant (see Table 3).

In non-exposed children in the control group, ADHD symptoms increased significantly between ages 7 and 9, reaching levels similar to those in exposed children. The estimate of GBG on the slope of ADHD symptoms was negative and significant, indicating that the GBG intervention had a positive impact (see Table 3). The effect size (Cohen's d ; Cohen, 1988) of the mean difference in ADHD symptom score between GBG and control-group non-exposed children was .27. As Figure 3 shows, the GBG prevented the increase in ADHD symptoms found in the control group of non-exposed children. Non-exposed boys had higher levels of ADHD symptoms than non-exposed girls (see Table 3). Overall, 16% of the non-exposed control-group children had experimented with smoking by age 10 and 11 years. This percentage was reduced by half, to 8%, in non-exposed GBG children – a difference that was significant (see Table 3). Non-exposed boys, however, had a higher probability of early-onset experimentation with smoking than non-exposed girls (boys: 11% GBG, 22% controls; girls: 4% GBG, 9% controls).

Discussion

Previous studies have documented the hazardous influence of prenatal exposure to maternal smoking on child development. The aim of this study was to test whether prenatal smoking also moderated the impact of a universal preventive intervention on the development of ADHD symptoms, and the associated risk for early-onset experimentation with smoking in elementary schoolchildren.

These are the main conclusions. First, at entry to elementary school, prenatally exposed children had higher levels of teacher-rated ADHD symptoms. After

Table 3 Impact of male gender and GBG intervention on parameter estimates of the development of ADHD symptoms, probability of early-onset experimentation with smoking at age 10/11 for prenatally exposed and non-exposed children

Status	ADHD symptoms						Probability of early-onset experimentation with smoking ^a			
	Male gender				GBG		Male gender		GBG	
	Intercept		Slope		Slope					
	Est.	SE	Est.	SE	Est.	SE	Est.	SE	Est.	SE
Non-exposed ($n = 416$)	1.7	.3*	.1	.2	-.4	.1**	1.1	.3**	-.4	.1*
Exposed ($n = 92$)	.4	.8	.4	.4	.0	.3	1.0	.6	.4	.6

Note: ^aEstimates are on a logit scale. Abbreviations: ADHD = Attention-Deficit/Hyperactivity Disorder; GBG = Good Behavior Game; Est = estimate; SE = Standard Error. Interactions between gender and GBG and current paternal smoking and GBG were not significant at $p < .05$ and excluded from the model. * $p < .05$. ** $p < .01$.

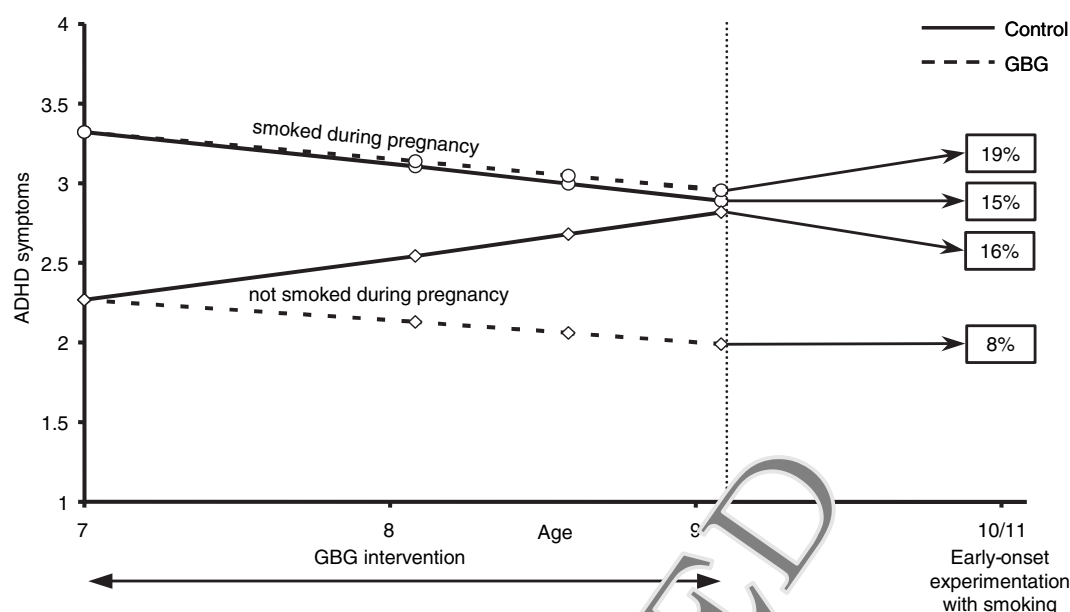


Figure 3 The development of ADHD symptoms and impact of GBG intervention from ages 7 to 9, and the probability of early-onset experimentation with smoking and GBG impact at age 10/11 for prenatally exposed and non-exposed children

controlling for a number of familial and socio-environmental risk factors that are known to be related to elevated disruptive behavior scores in children, this higher level of ADHD symptoms remained significant. This finding is in accordance with previous findings on ADHD (Linnet et al., 2003; Thapar et al., 2003).

Second, stable high levels of ADHD symptoms were found both in prenatally exposed control-group children and in intervention-group children. This indicates that prenatally exposed children were not susceptible to a positive impact of the intervention. Non-exposed control-group children started off with lower mean levels of ADHD symptoms than prenatally exposed children. From ages 7 to 9 years, these children showed a significant increase in ADHD symptoms, to levels that were similar to those in their prenatally exposed peers. This increase in ADHD symptoms from ages 7 to 9 years may reflect a normative growth in ADHD symptoms over these ages, as previously reported in a general Dutch population sample (Bongers, Koot, van der Ende, & Verhulst, 2003). Unlike prenatally exposed children, non-exposed children who received the intervention were receptive to its impact. In these children, the GBG prevented the – possibly normative – increase in ADHD symptoms found in non-exposed control-group children.

The growth in ADHD symptoms among non-exposed children who did not receive the GBG intervention warrants some further attention. Although, as stated above, it may reflect a normative growth in these symptoms in the studied period, it was somewhat surprising to see that this ‘normative’ growth was not observed among exposed children. One possible explanation for this finding might be that

exposed children had relatively extreme ADHD symptom scores at age 7 years. Subsequently, these children were unlikely to have increased scores with repeated assessments, which is referred to as regression to the mean (Cohen & Cohen, 1983). Other explanations should, however, be considered. To start with, ADHD symptom scores were only studied from age 7 to 9 years. It may well be that non-exposed children temporarily meet exposed children with respect to ADHD symptoms at this age, but that exposed children remain highly problematic after this age whereas low-risk children show declining levels of ADHD symptoms after age 9. In the study by Bongers et al. (2003), attention problems started to decline in late childhood and continued to decline in adolescence. In addition, only maternal smoking status during pregnancy was considered as the discriminator between the two trajectory groups. However, also given the correlation between prenatal smoking and other risk variables (e.g., parenting, SES), heterogeneity within this exposed group is likely. The stable levels of ADHD symptoms may therefore not be observed among each of the exposed children.

Our third finding was that children with high levels of ADHD symptoms at age 9 had the highest probability of early-onset experimentation with smoking at 10 and 11 years. Exposed children were always among this group with the highest probability at ages 10 and 11. In exposed-intervention children, the GBG had no influence on the probability of smoking. In non-exposed control-group children, whose levels of ADHD symptoms at age 9 were as high as those of prenatally exposed children, the probability of early-onset experimentation with smoking was as high as that in exposed children

aged 10 and 11. In contrast, in non-exposed intervention children who had lower levels of ADHD symptoms than their control group counterparts at age 9, the probability that they would experiment with smoking was 50% lower than in the non-exposed control-group children.

On the basis of these results, it can be concluded that the GBG can positively influence the developmental course of ADHD symptoms, and, as a possible consequence, the onset of experimentation with smoking. However, this effect was observed only among children who had not been prenatally exposed to maternal smoking.

With respect to gender, the fact that the developmental course of ADHD symptoms and early-onset experimentation of exposed children was similar for boys and girls corresponds only partly with previous studies on the effects of prenatal smoking on childhood behavior problems. For instance, several authors have reported that the effects on childhood conduct problems were as marked for girls as for boys (Maughan, Taylor, Taylor, Butler, & Bynner, 2001). Others, however, found that, during middle childhood, exposed boys were significantly more likely to develop conduct problems than girls (Rodriguez & Bohlin, 2005; Wakschlag & Hans, 2002); non-exposed boys had higher levels of ADHD symptoms and a higher probability of early-onset experimentation with smoking than non-exposed girls.

While the findings of this study should be regarded in the context of several limitations, we should first state that we had two reasons for choosing to focus on ADHD symptoms as the outcome of interest, rather than on oppositional defiant problems or conduct problems. First, of all the behavioral problems associated with prenatal exposure to maternal smoking, ADHD symptoms are among those most frequently studied (Linnet et al., 2003). Second, ADHD is the most commonly diagnosed childhood psychiatric disorder (American Psychiatric Association, 1994). However, the co-occurrence of ADHD symptoms with oppositional defiant problems and conduct problems in our studied period is substantial (Loeber, Green, Lahey, Frick, & McBurnett, 2000). This implies that prenatal smoking may also be a moderator of intervention success with respect to symptoms of oppositional defiant problems or conduct problems. Additionally, ADHD has been characterized as a disorder of notable heterogeneity in its composition, with symptom dimensions of hyperactivity, impulsivity, and inattention (Burke, Loeber, & Lahey, 2001). Given this heterogeneity, prenatal exposure to maternal smoking may not be a moderator of intervention effectiveness in each of these symptom dimensions. Testing each of these hypotheses was beyond the scope of this manuscript, but clearly warrants further investigation.

This study had a number of limitations. A concern is the fact that no data were available on the IQs or

cognitive abilities of the children. It was therefore not possible to examine whether learning difficulties or lower cognitive abilities made some children less receptive to the GBG.

Another limitation concerned the use of retrospective maternal reports of smoking during pregnancy. Although these may have involved a higher likelihood of recall bias, Maughan et al. (2004) found similar percentages of smoking during pregnancy rated only one year after birth. Moreover, our percentage was approximately similar to that of mothers who reported having smoked during pregnancy in the Netherlands (Crone et al., 2000). Related to this is the problem of rater bias: the risk that, due to the stigma associated with substance-use during pregnancy, self-reported smoking data may in this case not reflect actual smoking behavior. We tried to overcome this problem by using different time-points in our assessment of child behavior problems and women's use of cigarettes during pregnancy. It has also been suggested that, when pregnancy has passed and there is no apparent major adverse effect on the child, a mother may be more forthright in her reporting (Williams et al., 1998).

Also, teachers who implemented the GBG intervention were also the source of the children's outcome ratings. In other words, the fact that they were not blind to intervention may have led them to underreport the ADHD symptoms. In our view, because a class generally had a new teacher at the start of each grade, the severity of this limitation should not be overestimated, especially as the average assessment of the level of ADHD symptoms and of the impact of the GBG intervention on these ADHD symptoms is the product of a consensus of three different teachers per class.

Finally, in line with the fetal programming hypothesis we expected prenatal smoking effects also to be present at age 9. However, our results showed that exposed children started off with higher mean levels of ADHD symptoms than non-exposed children at age 7, but ended up with levels similar to those in non-exposed control-group children at age 9. Keeping the points with regard to growth in ADHD symptoms among non-exposed controls as discussed earlier in mind, this age-specific finding provides some support for the hypothesis of Maughan et al. (2004), who argued that the effects of prenatal smoking should be most evident in early childhood, and that older samples would highlight different patterns of effects; more research is needed to test the tenability of the fetal programming hypothesis in different age samples.

Given these caveats, the core conclusion of our analyses is that the consequence of prenatal exposure to maternal smoking is in accordance with the hypothesis that fetal programming may underlie the higher levels of ADHD symptoms at entry to elementary school. The intervention had no impact

on the course of ADHD symptoms, nor on the probability that exposed children would engage in early-onset experimentation with smoking. In contrast, non-exposed children entered elementary school with lower levels of ADHD symptoms and were receptive to the environmental intervention. It may be argued that the intervention merely prevented a normative growth in ADHD symptoms, and that the size of the effect was modest. However, there are three reasons why these results should not be underestimated. First, the non-exposed group consisted of 82% of the total sample. It is therefore reasonable to assume that the reason that not all these children improved on their ADHD symptoms is because their levels of such problems were already low. Instead, these results were probably due to a sub-sample within this non-exposed group, whose improvement was likely to have been much larger than the improvement found overall. Second, ADHD symptoms are highly predictive of a number of serious negative outcomes, including antisocial behavior, delinquency, conduct disorder and antisocial personality disorder (American Psychiatric Association, 1994). Third, early experimentation with smoking is predictive of prolonged smoking, possibly through the impact on the still-developing brain (Di Franza et al., 2000). The GBG intervention reduced the rate of smoking in childhood among non-exposed children by 50%.

Although, like previous studies, this study associates prenatal exposure to maternal smoking with elevated symptoms of ADHD in children, a key obstacle to interpreting this association is that there has been no unequivocal demonstration of a direct causal link (Thapar et al., 2003). By demonstrating that a randomized controlled promotive factor for behavioral adjustment was successful only among children who had not been prenatally exposed to maternal smoking, this study has gone beyond previous correlational studies on the hazardous influence of prenatal smoking. We could not, however, control for genetic influences, such as a familial history of ADHD, nor did we directly target the risk variable (prenatal smoking). Therefore, we cannot rule out the possibility that the genes that are associated with smoking during pregnancy are also transferred to the child, in whom they then cause ADHD symptoms. Neither can we prove that reductions in prenatal smoking due to intervention are associated with reductions in ADHD symptoms. With regard to genetic influences in this association, two previous studies (Maughan et al., 2004; Thapar et al., 2003) used genetically sensitive designs to control for them. Each found that there was a significant association between prenatal exposure to maternal smoking and offspring behavioral outcomes in addition to genetic and other environmental risk variables.

In sum, this study supported the entrenched and harmful role prenatal smoking plays in the etiology

of ADHD symptoms by showing that individual changes in ADHD symptoms due to a randomized delivered promotive factor took place only among children who had not been prenatally exposed to smoking. However, future research should explore whether prenatal smoking is a proxy measure that indexes another risk factor, or a causal factor for adverse developmental outcomes. In addition to the previous studies using genetic informative samples, intervention studies aimed at reducing prenatal smoking should be undertaken.

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References

- Achenbach, T.M. (1991). *Manual for the Teacher's Report Form and 1991 Profile*. Burlington, VT: University of Vermont.
- American Psychiatric Association. (1994). *Diagnostic and statistical manual of mental disorders* (4th edn). Washington, DC: American Psychiatric Association.
- Barker, D.J.P. (1998). *In utero* programming of chronic disease. *Clinical Science*, 95, 115–128.
- Bongers, I.L., Koot, H.M., van der Ende, J., & Verhulst, F.C. (2003). The normative development of child and adolescent problem behavior. *Journal of Abnormal Psychology*, 112, 179–192.
- Brennan, P.A., Grekin, E.R., Mortensen, E.L., & Mednick, S.A. (2002). Relationship of maternal smoking during pregnancy with criminal arrest and hospitalization for substance abuse in male and female adult offspring. *American Journal of Psychiatry*, 159, 48–54.
- Burke, J.D., Loeber, R., & Lahey, B.B. (2001). Which aspects of ADHD are associated with tobacco use in early adolescence? *Journal of Child Psychology and Psychiatry*, 42, 493–502.
- Button, T.M.M., Thapar, A., & McGuffin, P. (2005). Relationship between antisocial behaviour, attention-deficit hyperactivity disorder and maternal prenatal smoking. *British Journal of Psychiatry*, 187, 155–160.
- Cohen, J. (1988). *Statistical power analysis for the behavioral sciences* (2nd edn.). Hillsdale, NJ: Lawrence Erlbaum Associates.

- Cohen, J., & Cohen, P. (1983). *Applied multiple regression/correlation analysis for the behavioral sciences*. Hillsdale, NJ: Erlbaum.
- Cornelius, M.D., Leech, S.L., Goldschmidt, L., & Day, N.L. (2000). Prenatal tobacco exposure: Is it a risk factor for early tobacco experimentation? *Nicotine & Tobacco Research*, 2, 45–52.
- Crone, M.R., Hirasong, R.A., & Burgmeijer, R.J.F. (2000). Prevalence of passive smoking in infancy in the Netherlands. *Patient Education and Counseling*, 39, 149–153.
- Di Franza, J.R., Rigotti, N.A., McNeill, A.D., Ockene, J.K., Savageau, J.A., St Cyr, D., et al. (2000). Initial symptoms of nicotine dependence in adolescents. *Tobacco Control*, 9, 313–319.
- Dolan, L.J., Jaylan, T., Werthamer, L., & Kellam, S. (1989). *The Good Behavior Game manual*. Baltimore, MD: The Johns Hopkins Prevention Research Center.
- Erasmus MC. (2002). *Substance Use During Pregnancy Interview*. Rotterdam: Department of Child and Adolescent Psychiatry.
- Erasmus MC. (2000a). *Problem Behavior at School Interview*. Rotterdam: Department of Child and Adolescent Psychiatry.
- Erasmus MC. (2000b). *Substance Use Questionnaire*. Rotterdam: Department of Child and Adolescent Psychiatry.
- Ernst, M., Moolchan, E.T., & Robinson, M.L. (2001). Behavioral and neural consequences of prenatal exposure to nicotine. *Journal of the American Academy of Child and Adolescent Psychiatry*, 40, 630–641.
- Goldberg D.P. (1972). *The detection of psychiatric illness by questionnaire*. Windsor: Nfer Nelson.
- Goldberg, D.P., & Williams, P. (1988). *A users guide to the General Health Questionnaire*. Windsor: Nfer Nelson.
- Ialongo, N.S., Poduska, J., Werthamer, L., & Kellam, S. (2001). The distal impact of two first-grade preventive interventions on conduct problems and disorder in early adolescence. *Journal of Emotional and Behavioral Disorders*, 9, 146–160.
- Koeter, M.W.J., & Ormel, J. (1991). *General Health Questionnaire. Nederlandse bewerking Handleiding*. Lisse: Swets and Zeitlinger.
- Linnet, K.M., Dalsgaard, S., Obel, C., Wisborg, K., Henriksen, T.B., Rodriguez, A., et al. (2003). Maternal lifestyle factors in pregnancy risk of attention deficit hyperactivity disorder and associated behaviors: Review of the current evidence. *American Journal of Psychiatry*, 160, 1028–1040.
- Loeber, R., Green, S.M., Lahey, B.B., Frick, P.J., & McBurnett, K. (2000). Findings on disruptive behavior disorders from the first decade of the Developmental Trends Study. *Clinical Child and Family Psychology Review*, 3, 37–60.
- Maughan, B., Taylor, A., Caspi, A., & Moffitt, T.E. (2004). Prenatal smoking and early childhood conduct problems: Testing genetic and environmental explanations of the association. *Archives of General Psychiatry*, 61, 836–843.
- Maughan, B., Taylor, C., Taylor, A., Butler, N., & Bynner, J. (2001). Pregnancy smoking and childhood conduct problems: A causal association? *Journal of Child Psychology and Psychiatry*, 42, 1021–1028.
- Milberger, S., Biederman, F., Faraone, S.V., Chen, L., & Jones, J. (1997). ADHD is associated with early initiation of cigarette smoking in children and adolescents. *Journal of the American Academy of Child and Adolescent Psychiatry*, 36, 37–44.
- Monshouwer, K., van Dorsselaer, S., Gorter, A., Verdurmen, J., Vollebergh, W. (2004). *Jeugd en riskant gedrag: Kerngegevens uit het peilstationsonderzoek 2003. Roken, drinken, drugsgebruik en gokken onder scholieren vanaf tien jaar*. Utrecht: Trimbos Instituut.
- Muthén, B.O. (2001). Second-generation structural equation modeling with a combination of categorical and continuous latent variables: New opportunities for latent class-latent growth modeling. In L.M. Collins & A.G. Sayer (Eds.), *New methods for the analysis of change. Decade of behavior* (pp. 291–322). American Psychological Association: Washington, DC.
- Muthén, B.O. (2002). General growth mixture modeling for randomized preventive interventions. *Biostatistics*, 3, 459–475.
- Muthén, L.K., & Muthén, B.O. (1998–2004). *Mplus. Statistical analyses with latent variables. User's guide 3.0*. Los Angeles: Muthén & Muthén.
- Pauly, J.R., Sparks, J.A., Hauser, K.F., & Pauly, T.H. (2004). In utero nicotine exposure causes persistent, gender-dependant changes in locomotor activity and sensitivity to nicotine in C57Bl/6 mice. *International Journal of Developmental Neuroscience*, 22, 329–337.
- Rodriguez, A., & Bohlin, G. (2005). Are maternal smoking and stress during pregnancy related to ADHD symptoms in children? *Journal of Child Psychology and Psychiatry*, 46, 246–254.
- Rutter, M. (2002). Development and psychopathology. In M. Rutter & E. Taylor (Eds.), *Child and adolescent psychiatry* (pp. 309–324). Oxford, England: Blackwell Scientific Publications.
- Shelton, K.K., Frick, P.J., & Wootton, J. (1996). Assessment of parenting practices in families of elementary school-age children. *Journal of Clinical Child Psychology*, 25, 317–329.
- Slotkin, T.A., Seidler, F.J., Qiao, D., Aldridge, J.E., Tate, C.A., Cousins, M.M., et al. (2005). Effects of prenatal nicotine exposure on primate brain development and attempted amelioration with supplemental Choline or vitamin C: Neurotransmitter receptors, cell signaling and cell development biomarkers in fetal brain regions of Rhesus monkeys. *Neuropsychopharmacology*, 30, 129–144.
- Statistics Netherlands. (1999). *Standaard Beroepenclassificatie 1999* [Standardized Classification of Occupations]. Voorburg/Heerlen: Statistics Netherlands.
- Storr, C.L., Ialongo, N.S., Kellam, S.G., & Anthony, J.C. (2002). A randomized controlled trial of two primary school intervention strategies to prevent early onset tobacco smoking. *Drug and Alcohol Dependence*, 66, 51–60.
- Thapar, A., Fowler, T., Rice, F., Scourfield, J., van den Bree, M., Thomas, H., et al. (2003). Maternal smoking during pregnancy and attention deficit hyperactivity disorder symptoms in offspring. *American Journal of Psychiatry*, 160, 1985–1989.
- Thapar, A., Holmes, J., Poulton, K., & Harrington, R. (1999). Genetic basis of attention deficit and hyperactivity. *British Journal of Psychiatry*, 174, 105–111.

- Van der Sar, A.M., & Goudswaard, M. (2001). *Docentenhandleiding Taakspel voor basisonderwijs*. Rotterdam: Pedologisch Instituut.
- Van Lier, P.A.C., Muthén, B.O., van der Sar, R.M., & Crijnen, A.A.M. (2004). Preventing disruptive behavior in elementary schoolchildren: Impact of a universal, classroom based intervention. *Journal of Consulting and Clinical Psychology*, 72, 467–478.
- Van Lier, P.A.C., Vuijk, P., & Crijnen, A.A.M. (2005). Understanding mechanisms of change in the development of antisocial behavior: The impact of a universal intervention. *Journal of Abnormal Child Psychology*, 33, 521–535.
- Verhulst, F.C., van der Ende, J., & Koot, H.M. (1997). *Handleiding voor de Teacher's Report Form*. Rotterdam: Department of Child and Adolescent Psychiatry.
- Wakschlag, L.S., & Hans S.L. (2002). Maternal smoking during pregnancy and conduct problems in high-risk youth: A developmental framework. *Development and Psychopathology*, 14, 351–369.
- Wakschlag, L.S., Pickett, K.E., Cook, E., Benowitz, N.L., & Leventhal, B.L. (2002). Maternal smoking during pregnancy and severe antisocial behavior in offspring: A review. *American Journal of Public Health*, 92, 966–974.
- Williams, G.M., O'Callaghan, M., Najman, J.M., Bor, W., Andersen, M.J., Richards, D., et al. (1998). Maternal cigarette smoking and child psychiatric morbidity: A longitudinal study. *Pediatrics*, 102, 1–8.

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